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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/552,949 | OMARY ET AL. | |
| | Examiner | Art Unit | |
| | Carla Myers | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3,6 and 7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 6 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 28, 2009 has been entered.

2. Applicant's arguments and amendments to the claims presented in the response of July 28, 2009 and April 29, 2009 have been fully considered but are not persuasive to place all claims in condition for allowance. All rejections not reiterated herein are hereby withdrawn.

3. Claims 1, 3, 6 and 7 are pending.

It is noted that claim 1 has been examined herein to the extent that the claim reads on the elected methods which detect a genotype of K8 by assaying nucleic acids for the K8 R340H mutation. The non-elected subject matter of methods which assay for a mutation in a protein and which assay for the additionally recited non-elected mutations are withdrawn from consideration as being drawn to a non-elected invention.

### Claim Objections

4. Claim 1 is objected to because the claim includes subject matter of the non-elected inventions, namely the detection of the mutations other than K8 R340X and methods which assay for a mutation in a protein.

**Response to Remarks:**

In the response, Applicants state that claim 1 has not been further limited "in view of the previous species election, as the claim shall be restricted to this species if no generic claim is finally held allowable."

Applicant's response has been fully considered. However, no claims are pending which are generic and in particular claim 1 is not a generic claim - e.g., a claim to a method which detects any mutation in the K8 gene. Rather, claim 1 recites specific mutations that are structurally and functionally distinct one another. As the mutations do not share both a common structure and function, they are not of a similar nature and do not share a corresponding technical feature. As indicated in the restriction requirement of March 19, 2008, the non-elected mutations would only be considered for rejoinder with the elected K8 R340H mutation upon the allowance of a generic claim.

**Maintained Rejections**

**Claim Rejections - 35 USC § 112 second paragraph**

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 3, 6 and 7 are indefinite over the recitation of "a mutation at position 340 of keratin K8 from CGT-> CAT." The position of 340 in keratin is in reference to the keratin protein, however CGT -> CAT refers to a nucleotide sequence. Thereby, it is

unclear as to what is intended to be meant by the CGT->CAT mutation occurring at position 340 of the K8 protein.

B. Claims 3, 6 and 7 are indefinite because the claims refer to a step of analyzing for a change in a "codon genotype," but then recite that a mutation at position 340 is associated with predisposition to viral hepatitis or acute fulminant hepatitis. The claims do not set forth the relationship between the "codon genotype" and the mutation and thereby it is unclear as to how the step of analyzing for a change in a "codon genotype" is intended to result in a method wherein a mutation at position 340 is associated with a predisposition to noncryptogenic liver disease. Note that these rejections may be overcome by amendment of the claims to recite, for example, "analyzing nucleic acid of an individual human for a mutation in the nucleotide sequence of the keratin K8 gene encoding codon 340, wherein a CGT → CAT mutation in the nucleotide sequence of the keratin K8 gene encoding codon 340 indicates an increased risk for viral hepatitis or acute fulminant hepatitis in said individual human."

**Response to Remarks:**

In the response, Applicants state that the claims have been amended to recite that the change is a codon genotype encoding keratin K8 at position. However, this amendment does not overcome the rejection for the reasons discussed above.

**New Grounds of Rejections Necessitated by Applicant's Amendments to the Claims:**

C. Claims 3, 6 and 7 are indefinite over the recitation of "said predisposition to noncryptogenic liver disease" because this phrase lacks proper antecedent basis. This

rejection may be overcome by amendment of the claims to recite "said predisposition to increased risk for viral hepatitis or acute fulminant hepatitis."

**Claim Rejections - 35 USC § 112 – New Matter**

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 6 and 7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The specification as originally filed does not appear to provide support for the amendment to claim 1 to recite determining a change in a genotype of keratin relative to any wild-type sequence (i.e., any wild-type sequence of any gene). Further, the specification as originally filed does not appear to provide support for the amendment to claims 3, 6 and 7 to recite determining a change in a codon genotype relative to a wild-type sequence that encodes keratin K8.

The response points to page 5, lines 1-18 and page 24, lines 8 to the end of page of the specification as providing support for this amendment. However, page 5 teaches only comparing the K8 sequence of an individual to a "normal" K8 nucleic acid sequence. The specification does not define what constitutes a "normal" K8 nucleic acid sequence and does not specifically teach that a normal K8 nucleic acid is considered to

be a wild-type K8 nucleic acid. Page 24 of the specification teaches that two offspring had a wild-type K8 sequence as defined by the particular nucleotides encoding the amino acids at position 53, 61, 340, 433 and 465-468 and having the specifically recited sequence set forth in Table 5. Table 5 defines the wild-type keratin K8 protein as having an arginine at position 340. The specification teaches a wild-type K8 protein that has an arginine at position 340, but this teaching does not provide support for the distinct concept of a wild-type K8 protein having any other amino acid at position 340, or having any other amino acids at any other position in the protein. These teachings in the specification do not provide support for the broader concept encompassed by the claims of comparing the genotype of an individual with any wild-type sequence of any gene (claim 1) or with any wild-type sequence that encodes keratin K8 (claims 3, 6 and 7). This rejection may be overcome by amendment of claim 1, for example, to recite "analyzing a nucleic acid sample of an individual human for a mutation in the nucleotide sequence of the keratin K8 gene, wherein the mutation is a CGT → CAT mutation in the nucleotide sequence encoding codon 340 of keratin K8, and wherein the presence of said mutation indicates an increased risk for noncryptogenic liver disease in said individual human."

**Claim Rejections - 35 USC § 112 - Enablement**

7. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for identifying a human subject at increased risk for viral hepatitis or acute fulminant hepatitis (AFH) comprising: (a) providing a nucleic acid sample from said human subject wherein the nucleic acid sample comprises a nucleic

acid encoding keratin 8; (b) analyzing the sequence of the nucleic acid encoding keratin K8 to determine the identity of the nucleotides encoding codon 340; and (c) determining that said human subject has an increased risk for viral hepatitis or AFH if said human subject has the sequence CAT at codon 340 of the nucleic acid encoding keratin 8 as compared to a human subject that has the sequence CGT at codon 340 of the nucleic acid encoding keratin 8, does not reasonably provide enablement for methods for determining a predisposition to any noncryptogenic liver disease by determining a mutation in the keratin 8 gene resulting in a R340H substitution. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection was previously presented in the Office action of January 29, 2009 and has been modified herein to address the amendments to the claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

**Breadth of the Claims:**

Claims 1 is drawn to methods for detecting a predisposition to any type of noncryptogenic liver disease comprising analyzing an individual for a change in a

genotype, wherein the change in genotype is a codon encoding a K8 R340H mutation, and wherein the change in the genotype is associated with a predisposition to a noncryptogenic liver disease.

The genus of noncryptogenic liver diseases is considered to be very large and includes diseases having significantly different symptoms and etiologies, such as the diseases of cystic fibrosis, any type of liver cancer, drug induced liver failure, autoimmune hepatitis, neonatal hepatitis, polycystic disease, parenteral nutrition-induced, multiple adenomas, and congenital hepatic fibrosis (see, e.g., Table 2 of the specification at page 21).

**Nature of the Invention**

The claims are drawn to methods for detecting a predisposition to a noncryptogenic liver disease by assaying for a mutation in the keratin 8 gene encoding for a change of an arginine to histidine at amino acid position 340 of the keratin 8 protein. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

**Teachings in the Specification and State of the Art:**

The specification (page 5) teaches that the keratin 8 nucleic acid sequence was known in the art at the time the invention was made and is provided in GenBank Accession No. NM_002273. The specification further teaches that the keratin 8 nucleic acid sequence is provided as SEQ ID NO: 3 and the amino acid sequence is provided as SEQ ID NO: 4 therein.

The specification teaches the results of a study in which 467 liver explants from patients having liver disease and 349 healthy control blood samples were analyzed for the presence of mutations in the K8 gene. Based on this analysis, the specification identified 14 mutations that were present in the K8 gene – i.e., the mutations encoding for mutations: G52V, Y53H, G61C, R340H, G433S, R453C, I-465(I) RDT (468), I62V, L71L (CTG to CTA), A318S, R201C (CGC to TGC), E376E (GAG to GAA), V460M and V479I (see Table 3). The I62V, A318S, R201C (CGC to TGC), V460M and V479I are described as polymorphisms that are found at similar or higher incidence in controls as compared with individuals having liver disease (see footnote to Table 3). Nine of the mutations are characterized as posing "a potential risk factor for subsequent development of liver cancer" (see footnote for Table 3). However, 3 of these mutations, namely the G52V, R453C and I-465(I) RDT(468) mutations, were found in only a single patient (i.e., 1 out of 467 patients) having liver disease. While the 3 mutations were not found in any of the 349 control blood samples, no results are provided for control liver samples. Given the fact that the 3 mutations were found in only a single patient and that the sample control population was not of an equivalent size as compared to the affected patient population and that no control liver samples were analyzed, the results obtained from this analysis would not be accepted by those of skill in the art as providing a conclusive correlation between the presence of the mutations and liver disease.

With respect to the elected mutation, the specification teaches that the C<u>G</u>T to C<u>A</u>T mutation encoding for an Arg to His substitution at codon 340 was present in 30/467 (6.4%) human subjects having liver disease and in 10/349 (2.9%) control human

subjects (Table 3). The specification further teaches that the K8 R340H mutation was found in human patients having viral hepatitis and in patients with acute fulminant hepatitis (AFH; Table 4). Accordingly, the specification has enabled methods of determining whether a human patient has a predisposition to viral hepatitis or AFH by detecting the K8 R340H mutation. However, the specification has not enabled methods for detecting the R340H mutation as indicative of any other noncryptogenic liver disease in human or nonhuman subjects.

**The Predictability or Unpredictability of the Art :**

Claim 1 is inclusive of methods which detect a predisposition to any type of noncryptogenic liver disease by assaying for a mutation encoding for an arg to his substitution at codon 340 of keratin 8. However, the data provided in the specification is limited to the detection of the R340H mutation in subjects having viral hepatitis or AFH. The specification does not teach the frequency of occurrence of the R340H mutation in other types of liver disease, such as cystic fibrosis or liver tumors. It is highly unpredictable as to whether the results obtained with one type of liver disease can be extrapolated to other types of liver disease.

The teachings in the specification support the unpredictability of establishing a correlation between a mutation/polymorphism and the occurrence of liver disease. In particular, the specification (table 3) teaches that while the I62V, A318S, R201C (CGC to TGC), V460M and V479I mutations were present in subjects having liver disease, these mutations were present at a similar or higher incidence in control subjects that do not have liver disease.

The teachings in the prior art support the unpredictability of extrapolating the findings of an association between a keratin 8 mutation and one type of liver disease to all other types of liver disease. In particular, by Ku et al (The New England Journal of Medicine, May 2001. 344: 1580-1587; cited in the IDS of November 17, 2005) detected the Gly61Cys and Tyr53His mutations in subjects having cryptogenic cirrhosis, but did not detect these mutations "in the patients with other liver diseases" (see abstract). The "other liver diseases" in which the mutations were not present include hepatitis C, autoimmune hepatitis, acute fulminant hepatitis, primary bilary cirrhosis, Wilson's disease, hepatitis B and neonatal hepatitis (page 1581, para 1).

Moreover, it is well recognized in the art that the associations between polymorphisms and phenotypic traits are often irreproducible. For example, Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

The post-filing date art supports the unpredictability of detecting mutations in the keratin 8 gene as diagnostic of a predisposition to liver disease. For example, Hesse (Journal of Medical Genetics. 2004. 41: e42) analyzed the keratin 8 gene in 256 European Caucasians having diverse liver diseases, but did not detect any amino acid altering mutations in these subjects. A g.740A>G variation was detected in both patients with liver disease and in control subjects. A g.418-4C>G mutation in intron 1 was also detected, but only in one patient with HBV (see page 2, col. 2). Hesse concluded that "(t)he contrary result of our study to the mutations reported so far suggests that allele frequencies might possibly differ between European and North American populations. It might be also possible that additional risk factors coincide with K8 and K18 mutations in Northern American but not European liver patients" (page 3, col. 1).

Similarly, Halangk et al (Journal of Medical Genetics. 2004. 41: e92) studied the prevalence of Y54H and G62C keratin 8 mutations in a population of 1668 patients with liver disease and 679 healthy controls. Halangk did not find an association between the occurrence of these mutations and cryptogenic or noncryptogenic liver disease (page 2, col. 2). The authors indicated that one reason for the discrepancy in the results with those of prior studies may be the fact that their study analyzed subjects having a greater ethnic homogeneity (page 2, final para to page 3, first para).

There is no showing or evidence which links particular nucleotides in the keratin 8 gene with particular functional properties correlated with liver disease. The specification (page 27) discusses the potential effects of 4 of the mutations. Namely, the specification suggests that the R340H mutation may be correlated with destabilization,

the G433S mutation may be associated with altering keratin phosphorylation, the R453 mutation may be correlated with formation of a disulfide bond and the 1-465(I) RDT (468) mutation may be associated with destablilization. However, the specification does not teach any additional critical sequences or domains in keratin 8 that are required to impart the function of causing or otherwise being associated with any type of cryptogenic or noncryptogenic form of liver disease. The specification (page 28) also teaches that while there are a number of potential functions associated with keratin that may effect liver disease, "the mechanisms by which keratin mutations predispose to cirrhosis remain to be defined." Accordingly, in the absence of a clear structure-function relationship between the R340H keratin 8 mutation and the occurrence of a representative number of distinct noncryptogenic liver diseases, it is unpredictable if the presence of the R340H mutation can be detected as indicative of any type of noncryptogenic liver disease.

**Amount of Direction or Guidance Provided by the Specification and Degree of Experimentation:**

The specification does not provide sufficient guidance as to how to diagnose a predisposition to all noncryptogenic liver diseases by assaying for a mutation at position 340 of the keratin K8 protein. Extensive experimentation would be required to identify additional noncryptogenic liver diseases associated with the CGT to CAT mutation at codon 340 of keratin 8. For example, such experimentation may involve sequencing the keratin 8 gene of individuals having cystic fibrosis to determine if the CGT to CAT mutation at codon 8 is present, sequencing the keratin 8 gene of

individuals that do not have cystic fibrosis, determining the frequency of the CGT to CAT mutation at codon 340 in the individuals having cystic fibrosis and not present in individuals that do not have cystic fibrosis, and performing a statistical analysis to determine whether there is a statistically significant increase or decrease in the occurrence of the mutation in individuals having cystic fibrosis as compared to individuals that have not had cystic fibrosis. Further experimentation may also include performing the above method in a representative number of human subjects having and not having other forms of noncryptogenic liver disease, such as cirrhosis, neonatal hepatitis, liver cancer etc. Because the outcome of such experimentation cannot be predicted, such experimentation is considered to be undue.

While methods for sequencing nucleic acids are known in the art, such methods provide only the general guidelines that allow researchers to randomly search for polymorphisms that may linked to a particular phenotype. The results of performing such methodology are highly unpredictable. The specification has provided only an invitation to experiment. The specification does not provide a predictable means for determining that the R340H mutation is associated with noncryptogenic liver disease in general or for identifying other particular types of noncryptogenic liver diseases which are associated with the occurrence of the R340H mutation.

**Working Examples:**

The specification provides a working example in which human subjects having viral hepatitis or AFH were genotyped for a mutation in the sequence of the keratin 8

gene encoding codon 340, and the presence of a mutation encoding for a histidine at codon 340 was detected.

However, no working examples are provided wherein the R340H mutation is detected as indicative of other types of liver disease, such as neonatal hepatitis, or liver cancer, or Wilson's disease, or cystic fibrosis or polycystic disease or hepatic artery thrombosis, etc.

**Conclusions:**

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification teaches an association only between the CGT CAT mutation encoding for an Arg to His substitution at codon 340 of keratin K8 and the occurrence of viral hepatitis or AFH in human subjects, whereas the claims encompass

methods for detecting this mutation as indicative of all types of noncryptogenic liver disease or as indicative of other specific types of noncryptogenic liver disease in a human subject. The specification does not teach a representative number of different types of noncryptogenic liver diseases, other than viral hepatitis or AFH, which are correlated with the occurrence of the R340H mutation. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

**Response to Remarks:**

In the response, Applicants traversed this rejection by stating that they have previously submitted data from the present inventors regarding the importance of keratin 8 variants in acute liver failure and the importance of some K8 variants in African Americans with liver disease and African Americans in general. It is stated that a copy of the data is attached that the data has been submitted to the New England Journal of Medicine.

It is acknowledged that Applicants have now submitted a complete copy of the reference to which Applicants previously provided a copy of an abstract. However, the copy of the reference submitted to the New England Journal of Medicine is Applicants own reference. Thus, this information is not impartial in nature and does not serve as evidence to establish the enablement of the present invention. MPEP 716.02 states that "The reason for requiring evidence in declaration or affidavit form is to obtain the

assurances that any statements or representations made are correct, as provided by 35 U.S.C. 25 and 18 U.S.C. 1001." Permitting a publication to substitute for expert testimony would circumvent the guarantees built into the statute. Ex parte Gray, 10 USPQ2d 1922, 1928 (Bd. Pat. App. & Inter. 1989). Accordingly, the information set forth in the submitted reference cannot be relied upon to establish enablement of the claimed invention because it has not been provided in declaratory form.

Further, the submitted reference teaches that the "R341H mutation" was associated with acute liver failure in Caucasians, but does not establish a general role for this mutation in noncryptogenic liver disease such that one could extrapolate the findings obtained with acute liver failure to any noncryptogenic liver disease. For example, it remains unclear as to how the association between the mutation and acute liver failure results in the conclusion that the mutation causes or is otherwise indicative of a predisposition to developing liver cancer given the distinct underlying molecular processes associated with acute liver failure as compared to liver cancer.

Applicants state that the mutations in K8 have an "underlying molecular logic, " such as the destablization of a protein. Applicants point to the teachings of Ku et al (2002. Gastroenterology) as stating that there is an "extensive body of transgenic animal data showing that keratins play an essential role in protecting hepatocytes from mechanical and nonmechanical stresses." However, the Ku et al paper also constitutes Applicants own work. It is not considered to be impartial in nature and thereby cannot be relied upon to establish enablement of the claimed invention. Additionally, the response does not establish that the R340H mutation alters the functional activity of

keratin K8 in a manner that effects hepatocytes from mechanical and nonmechanical stresses, as would be necessary to support the contention that this mutation is associated with noncryptogenic liver diseases in general.

Applicants point to Table 6 (page 27 of the specification ) as teaching the molecular consequences of the keratin mutations. This table indicates that the R340H mutation has the "potential effects" of destabilization. The table does not indicate what is destabilized. Further, while the table lists the potential effect, the table and specification do not in fact establish or provide any type of evidence to show that the mutation in fact has this effect. Most importantly, the specification and response do not explain why this potential effect of destabilization would be expected to cause or otherwise be associated with a representative number of noncryptogenic liver diseases.

Applicants assert that K8 R340H has been shown to be a mutation hot spot. However, the specification and response do not explain why or provide any type of evidence to support an assertion that a mutation hot spot would necessarily be correlated with all types of noncryptogenic liver diseases or other types of liver disease. The response asserts that the claims meet the enablement requirement because the specification teaches how to determine the sequence of a polynucleotide and that this requires only routine experimentation. This argument is not persuasive because the claims are not directed to general methods for determining the nucleotide sequence of a K8 polynucleotide. Rather, the claims are directed to methods for determining a predisposition to any particular or to all non-cryptogenic liver diseases. Further, it is maintained that the experimentation is undue because the results of such

experimentation are highly unpredictable, for the reasons discussed in detail above. For example, Ku (May 2001) was cited in the above rejection as teaching that while the Gly61Cys and Tyr53His mutations were detected in patients having cryptogenic cirrhosis, these mutations were not detected "in the patients with other liver diseases" (see abstract). The "other liver diseases" in which the mutations were not present include hepatitis C, autoimmune hepatitis, acute fulminant hepatitis, primary bilary cirrhosis, Wilson's disease, hepatitis B and neonatal hepatitis (page 1581, para 1). The response does not specifically address this reference or this aspect of the rejection.

Applicants state that there may be some non-functional variants within the genus defined by the claims, but assert that Applicants are not required to establish that every species within a claimed genus will work. This argument has also been fully considered but is not persuasive. While Applicants are not required to establish that all species encompassed by the claims are operable, Applicants are required to establish the enablement of a representative number of species encompassed by the claims. In the present situation, Applicants have established an association only between the CGT to CAT mutation at the codon encoding position 340 of the K8 protein and the risk of viral hepatitis and acute fulminant hepatitis in human subjects. Establishing the enablement of 2 species (viral hepatitis and AFH) within a genus of thousands of possible species (i.e., any non-cryptogenic liver disease, including e.g., Wilson's disease, cystic fibrosis, primary oxalosis, Nieman-Pick, any liver cancer, any polycystic disease, carcinoid, biliary atresia, autoimmune hepatitis, neonatal hepatitis, etc) is not considered to be

sufficient to establish the enablement of a representative number of species within the broadly claimed genus.

The response states that the invention is not based only on association studies but is also based on animal models. However, the response does not point to any particular teachings in the specification of an animal model that establishes that the CGT to CAT mutation encoding codon 340 keratin K8 is associated with a representative number of distinct kinds of noncryptogenic liver diseases in human subjects.

The response cites the Board decision of Ex parte Walsh et al as "relevant to the facts of the present application." The response does not state how this decision is relevant to the facts of the present application. The decision in fact is limited to a finding that the claims are enabled to a method for screening for increased risk of prostate cancer by assaying for the presents of the R293X and D174Y mutations in the MSR1 based on the teachings in the specification therein of a relationship between the R293X and D174Y mutations. The fact pattern of the application upon which this decision was rendered are distinct from the present situation. In the cited decision, the R293X and D174Y mutations were detected in several families with familial and hereditary prostate cancer. Whereas, the present specification teaches only an association between the CGT to CAT mutation encoding codon 340 keratin K8 and viral hepatitis and acute fulminant hepatitis, but does not teach an associated between this mutation and a representative number of other distinct kinds of noncryptogenic liver diseases or with noncryptogenic liver disease in general. It is also noted that the genus of "prostate

cancer" includes sporadic and hereditary prostate cancer, and that these two types of cancer are significantly related with respect to their biological attributes. This is significantly distinct from the present situation wherein the claimed genus of noncryptogenic liver diseases includes a significantly large number of diverse diseases which differ from one another with respect to their etiology and symptoms. It has not been established that the R340H mutation has a common functional effect or role in the occurrence of a representative number of noncryptogenic liver diseases.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Carla Myers/

Primary Examiner, Art Unit 1634